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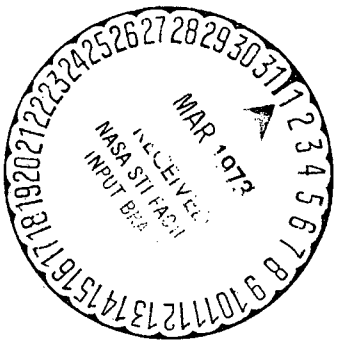
PHYSIOLOGICAL PROBLEMS OF PROLONGED WEIGHTLESSNESS

N. N. Gurovskiy and A. A. Kiselëv

Translation of "Fiziologicheskiye problemy dlitel'noy nevesomosti," Astronautica Acta, Vol. 17, 1972, pp. 79-88



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16. Abstract Two dogs, Ugolëk and Veterok, were exposed to weightlessness for about 22 days aboard the Soviet Cosmos 110 artificial satellite. Changes in cardiodynamics characterized as the functional hyperdynamia cordis syndrome were revealed. The functions of the digestive, motor, coagulative and other systems of the animals' organisms were investigated. Among the significant changes discovered were: a 30% loss in body weight; disturbances of ion equilibrium and related water loss; disturbed enzyme-forming function of the large intestine resulting in a sharp increase in the content of the intestinal enzymes enterokinase and alkaline phosphotase; 10-11% reduction in the mineral concentration in bone tissue; and decrease in lysozyme activity. The data indicate that space missions of relatively long duration (over 20 days) produce qualitatively new and more pronounced changes in the animal organism as compared to earlier flights of shorter duration.

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PHYSIOLOGICAL PROBLEMS OF PROLONGED WEIGHTLESSNESS

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The transition of human civilization to a new era, the era of going out beyond the bounds of the earth, presents biology and medicine with a multitude of complex and fundamentally new problems. The most pressing problem at present is that of prolonged weightlessness. An answer to the question of whether man will be able to remain in a state of weightlessness for a long time while maintaining a normal level of work capacity will determine to a considerable degree the possibility and further means of man's mastering outer space. /79*

Up to the present time, the possibility of a man staying 14 days under space flight conditions has been demonstrated by the flights of Soviet and American astronauts. Spaceship crew members have retained sufficient work capacity here to be able to control the ship, conduct scientific research, go out into open space and satisfactorily endure return to Earth. However results of postflight examinations of astronauts have proved highly alarming. Thus attention is drawn to development of orthostatic instability, dehydration of the organism developing even under conditions of unlimited intake of water, decalcination of bone tissue and some other disorders. Therefore the very cautious statements by some scientists in regard to the prognosis for tolerance of prolonged flight are not unexpected.

Paramount to solution of practical problems in the present stage of man's mastery of outer space is study of the fundamental problem of the principles of the human organism's functioning in the first phase of adaptation to weightlessness. Production of phenomenological events in the period of a comparatively long stay under conditions of weightlessness appear, in this connection, to be an independent and highly important division of the problem.

We think that material obtained in an experiment on the Cosmos-110 artificial earth satellite with two dogs, Ugolëk and Veterok, who were under weightless conditions for 22 days, will be of specific interest in this regard.

Without going into detail on the methodological side of the question, which has been illuminated in sufficient detail in the literature, we will present some data obtained in flight and in

*Numbers in the margin indicate pagination in the foreign text.

the postflight examination of the experimental animals.

One of the important aspects of the investigation was study of the circulatory apparatus under zero gravitation conditions. /80
The functioning of the cardiovascular system in the 22-day space flight was evaluated using a modified polycardiography method. Deciphering of polycardiograms (simultaneous recording of the ECG, sphygmogram and phonocardiogram) allowed us to quantitatively assess the contractile function of the myocardium by determining the duration of phases of the cardiac cycle.

Analysis of data on the cardiac cycle obtained in the period of the spaceship-satellite's orbital flight allowed us to discover change in the duration of the periods of expulsion and tension in the experimental animals. A tendency toward decrease in the duration of the period of expulsion was observed in both dogs toward the end of the flight. The duration of the period of tension always exceeded the original level, although it underwent various changes. Thus in the dog Ugolëk, the period of expulsion amounted to 180 ms before the flight and it decreased to 130 ms in the flight period; the period of tension was correspondingly 25 ms before the flight and varied within 90-60 ms during the flight (see Figs. 1 and 2).

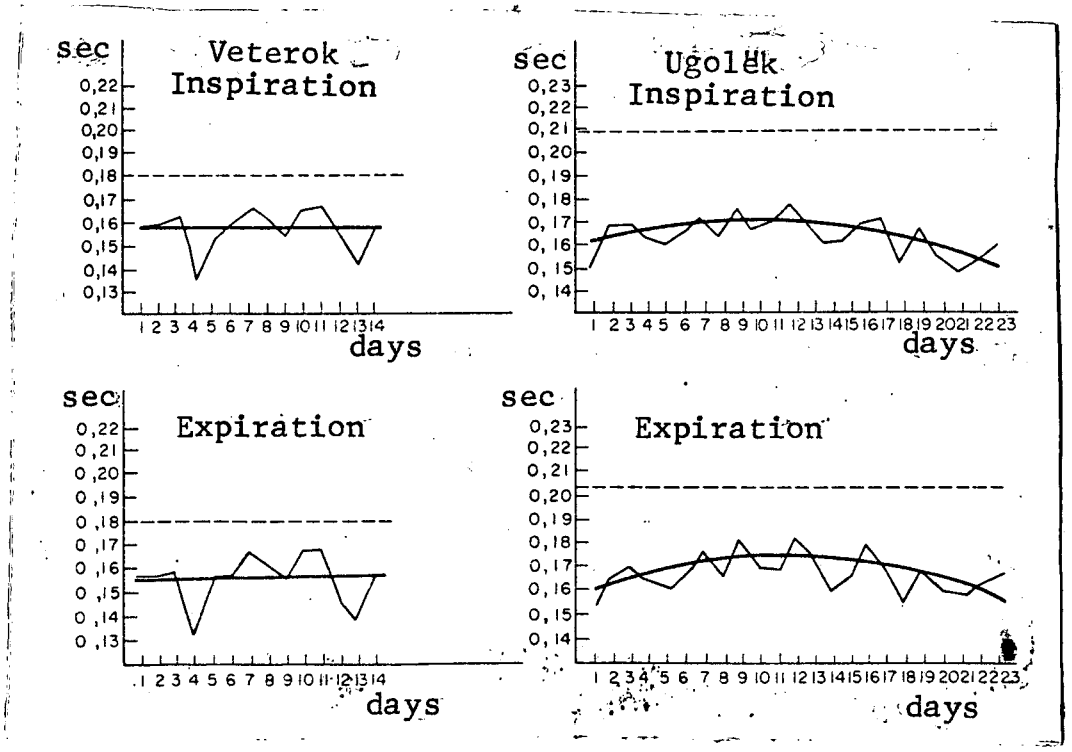

Fig. 1. Change in the duration of the period of expulsion in the dogs Veterok and Ugolëk during orbital flight.

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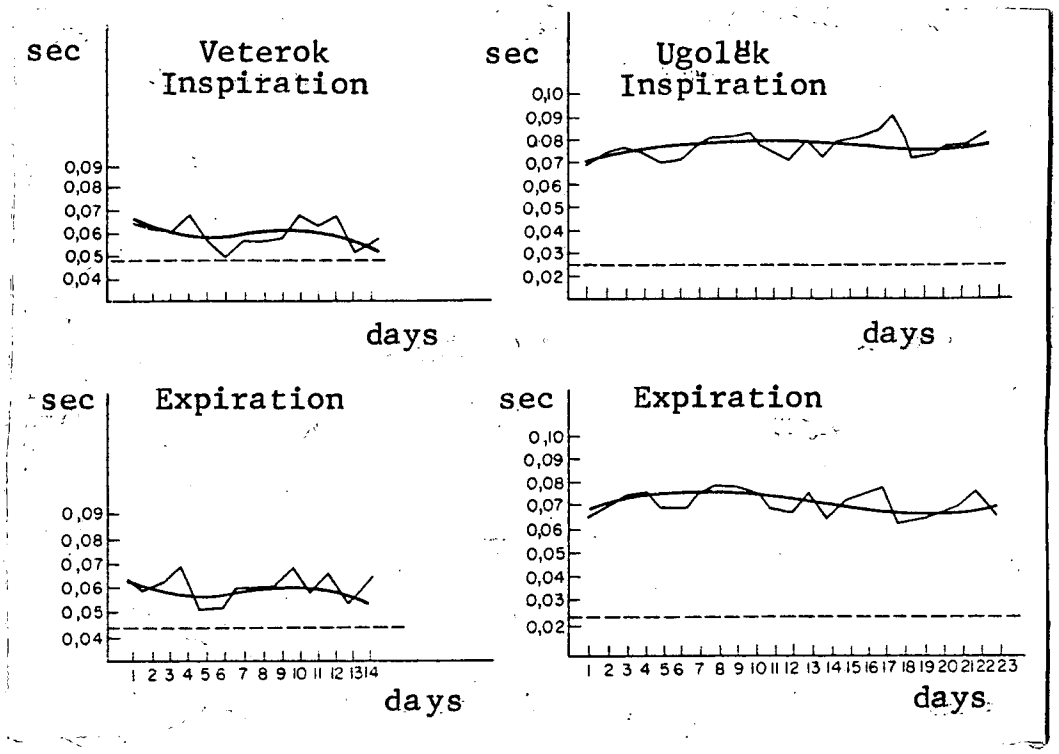

Fig. 2. Change in the duration of the period of tension in the dogs Veterok and Ugolëk during orbital flight.

Such change in cardiac activity may be characterized as the hypodynamia cordis syndrome encountered in clinical practice mainly in patients with disturbances of the contractile function of the myocardium in various ischemic states,(myocardial infarct, cardiosclerosis etc), as well as in functional hypodynamia as a result of insufficient cardiac filling under orthostatic influences or in the Valsalva test. The functional genesis of this syndrome seems more probable to us for flight conditions since restructuring of the phase structure of the cardiac cycle was noted in the dogs as early as in the first hours of zero gravitation's effect. No cardiographic signs of substantial disturbances of myocardial circulation, characteristic changes in the form of the ECG, extrasystolia etc were discovered in the animals here. /80

Therefore, the functional hypodynamia cordis syndrome in dogs may be attributed to change in the intra- and extracardiac conditions of the ventricles' activity.

In order to determine whether these disturbances in hemodynamics were the consequence of weightlessness and accompanying hypokinesia or of a whole complex of factors in space flight, a 22-day experiment was conducted on four dogs under ground conditions, an experiment completely repeating the research program carried out on the Cosmos-110 biosatellite. /81

Analysis of change in the phase structure of the cardiac cycle in the experimental animals here showed shortening of the duration of the period of expulsion in all four dogs. The duration of the period of tension exhibited a tendency toward increase. Therefore, only the changes in the period of expulsion were analogous to those that were observed in the prolonged orbital flight. The fact should also be noted that the dogs' condition after the laboratory experiment was considerably better than after the flight.

In connection with the fact that in this experiment we could not use direct methods for investigating hemodynamics, a physiological interpretation of the phase structure of the cardiac cycle was possible only on the basis of supplementary special experimental research and data from the literature.

The "discharging" nature of reflexes in weightlessness (Bayevskiy, R. M., Gazenko, O. G., 1964d) and the reduction in the organism's energy expenditures forced us to allot the greatest attention to study of conditions accompanying decrease in the volume of circulating blood and reduction in venous return and the filling of the ventricles of the heart.

In our opinion, the method of switching an apparatus into artificial circulation (AAC) into the greater circle of circulation is most convenient for creating and investigating various conditions of the left ventricle's functioning. Such a layout of an experiment allows one to regulate the amount of overall peripheral resistance, circulating volume and venous return to the heart (see Fig. 3). Here pressure was recorded in the aorta and in the vena cava inferior, as well as at the aortal valves; the phonocardiogram and the ECG, in the 11 standard leads; and the amount of volumetric blood flow, in the aorta. The state of cardiodynamics was investigated under the following influences:

1. Passive turning of a dog from the horizontal position to the verticle, head upwards;

2. In increase of the volume of circulating blood by introduction of blood into the greater circle of circulation from a storage vessel.

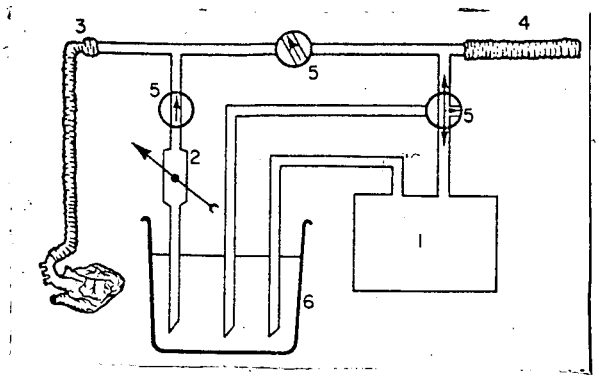

Fig. 3. Layout of the experiment using the AAC. 1. Apparatus for artificial circulation (AAC); 2. Imitator of hemodynamic resistance; 3. Central section of the aorta; 4. Peripheral section of the aorta; 5. Stopcock shutting off vascular stream; 6. Buffer storage vessel. /82

We processed the data obtained according to Blumberger's method, determining the duration of the cardiac cycle, the electromechanical systole and the electric and mechanical systoles; the duration of the asynchronous and isometric contractions and of periods of tension and expulsion; the magnitude of the mechanical coefficient; and a number of calculated indices. /81

The majority of authors explain the changes in cardiac activity observed in turning the body head upwards by decrease in venous return of blood to the heart as a result of redistribution of blood in the direction of the lower extremities and accumulation of it in dilated veins. According to the data of T. Wang (1960), the size of the stroke of volume decreases by 41% on the average in the orthostatic test. This is accompanied by reflex increase in the frequency of cardiac contractions aimed at maintaining normal minute heart volume. Decrease in systolic volume in an animal's transition from a horizontal to a verticle position with the head upwards is also noted in the experiment on dogs conducted by T. Hoffman et al (1965). Such reduction in venous return leads to reduced filling of the ventricles and decrease in the contractile capacity of the myocardium; a consequence of this is an increase in the duration of the period of isometric contraction. Both an absolute and a relative shortening of the duration of the period of expulsion takes place as a result of the reduction in stroke volume observed in this test. Analogous data were obtained in the experiments we conducted. The orthostatic test on a revolving table led in dogs to an increase in the period of tension from 96 to 120 ms and shortening of the period of expulsion from 171 to 140.1 ms after transfer to a verticle position. /82

Contrary changes in the specified parameters were observed in experiments in which the amount of circulating blood was increased by introducing it into the blood stream from a storage

vessel (see Fig. 4).

Change in the structure of cardiac contraction when conducting experiments with an AAC switched in. /83

Indices (in ms)	Orthostatic Test		Increase in the Volume of Circulating Blood	
	Horizontal Position	Verticle Position	Before	After
RR	460	470	400	470
RQ	99.0	97.5	225	238.5
QT	276.5	270.0	-	-
Q-ungrounded loop	110.3	134.6	-	-
Period of expulsion	171.0	140.0	182.0	205.2
Period of tension	96.0	120.0	64.0	45.0
Mechanical coefficient	1.78	1.20	2.86	4.56
Isometric contraction	34.0	60.0	-	-
Arterial pressure	143/99	97/92	-	-
Volumetric blood flow (in ms)	-	-	700	750

Fig. 4.

Consequently, in the absence of coarse disturbances of the contractile function of the myocardium, the amount of venous flow to the heart, by influencing filling of the ventricles, leads to quite specific changes in the structure of cardiac contractions. /82

On the basis of the results obtained, the following appear to us as the most probable causes of development of functional hypodynamia cordis:

1. Reduction in the volume of circulating blood;

2. Decrease in venous return and filling of the ventricles;

3. Probably, decrease in arterial pressure.

Other regularities can also be noted in the state of the circulatory apparatus and its regulation in experimental animals in the flight period: prevalance of tonus of the parasympathetic nervous system, tendency toward brachycardia, decrease in arterial pressure, variability of the RR interval and an inclination

toward vagal reactions.

Results of the Postflight Examination.

Pronounced discoordination of movements was noted in the animals in the first days after landing. They stumbled when walking and there were pronounced swinging movements of the head. However, these changes leveled out as early as on the third-fourth day.

Evidently such disturbances of coordination cannot be explained solely by the effects of hypokinesia and muscular atrophy. Possibly they are the result of a specific influence of weightlessness. Further research is necessary in this direction. /83

One of the most substantial changes discovered after completion of the flight was the animals' sharp loss in weight. One of the dogs lost 2.0 kg, which comprised 26.2% of its original weight; the second lost 2.4 kg, i.e. 29% of its weight before the flight, whereas analogous weight loss in the control experiment comprised no more than 0.5 kg (see Fig. 5). The dogs had recovered half of the weight lost 9-10 days after the flight. Further increase in weight took place slowly and complete recovery of it took place after more than 30 days. Calculation of extracellular fluid conducted according to Derreaux's method allowed us to establish that fluid loss comprised 45-50% of the overall weight loss. This can evidently explain the sufficiently rapid recovery of ½ of the lost weight after the flight. Moreover, the heightened amount of potassium and calcium in the animals' blood plasma, which reflects a significant shift in the electrolytic equilibrium of the organism, attracted attention.

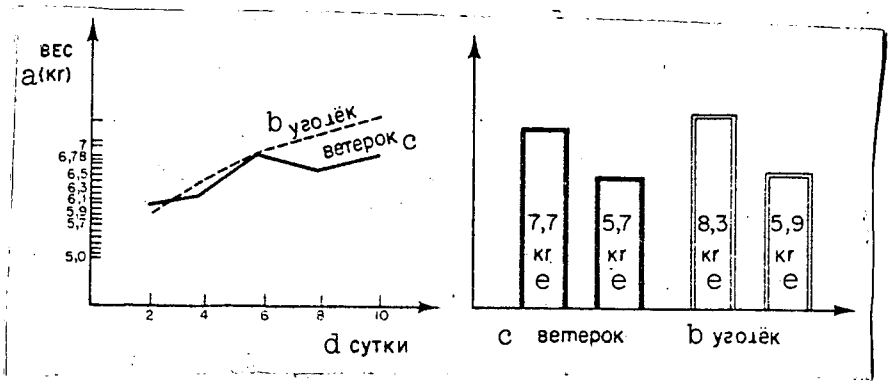

Fig. 5.

Key: a. weight (kg); b. Ugol'ëk; c. Veterok; d. days; e. kg.

Hematological examination of dogs that had completed a 22-day space flight.

	Veterok						Ugolëk				
	Before the Flight	Days after the Flight					Before the Flight	Days after the Flight			
		1	2	3	5	9		1	2	3	5
Hb (g%)	11,8	14,2	12,0	9,6	11,2	11,0	11,2	15,0	10,6	10,2	14,6
Erythrocytes	$3770 \cdot 10^3$	$4260 \cdot 10^3$	$3520 \cdot 10^3$	$2920 \cdot 10^3$	$3560 \cdot 10^3$	$5550 \cdot 10^3$	—	$5080 \cdot 10^3$	$2860 \cdot 10^3$	$3200 \cdot 10^3$	$4070 \cdot 10^3$
Leukocytes	10.200	13.200	16.800	27.450	26.500	29.200	9680	19.600	22.750	22.900	19.350
ROE (mm/hour)	16	31	40	52	44	47	6	40	39	33	45
Thrombocytes	$390 \cdot 10^3$	$900 \cdot 10^3$	$990 \cdot 10^3$	$990 \cdot 10^3$	$520 \cdot 10^3$	$620 \cdot 10^3$	—	$600 \cdot 10^3$	$680 \cdot 10^3$	$460 \cdot 10^3$	$520 \cdot 10^3$
Stabnuclears	23	25	22	25	17	14	7	26	27	30	16
Lymphocytes	5	10	7	20	34	14	25	16	3	7	11

Fig. 6.

Changes in the biochemical composition of dogs' blood in the postflight period.

	Albumins (%)		Globulins (%)		Sugar (Megagram %)		Cholestrrin (Megagram %)		Glutamic aspartic transaminase (Units)	
	Veterok	Ugolëk	Veterok	Ugolëk	Veterok	Ugolëk	Veterok	Ugolëk	Veterok	Ugolëk
Norm	56–66		34–44		80–120		140–180		20–40	
3rd-5th day	26	30	74	70	42	85	—	—	59	74
9th day	37	40	63	60	—	58	286	274	44	39
22nd day	35	38	65	62	34	52	146,7	166,7	28	29
30th day	34	38	66	62	74	57	—	—	—	—

Fig. 7.

Investigation of the peripheral blood allowed us to reveal in the experimental animals increase in the amount of hemoglobin and number of erythrocytes, acceleration of the ROE and a rise in the number of thrombocytes. Reduction in plasma volume (hematocrit indications) were also noted in both dogs (see Fig. 6). A relative decrease in blood serum albumins was also noted in both dogs in biochemical analysis. The relative quantity of globulins was increased, mainly due to the alpha- and beta-fractions. The quantity of gamma-globulins was essentially unchanged in the postflight period (see Fig. 7).

One of the indices characterizing the organism's resistance is change in lysozyme activity. Investigation of lysozyme activity of the gastric juice, blood serum, feces, urine and skin showed that the bacteriological activity of the gastric juice was significantly reduced in both dogs after completing the flight. Thus on the fourth day after the flight the lysozyme titer was lower than 1 : 20 whereas in control dogs on the same food ration on earth, the average lysozyme titer of the gastric juice amounted to 1 : 522. Normalization of lysozyme activity of the gastric juice of dogs that completed the flight took place only on day 16. The bacteriological activity of the blood serum was also depressed in them. This was expressed in low lysozyme titers amounting to 1 : 20, 1 : 30 and 1 : 45 in the first five days after the flight. In healthy normal dogs, lysozyme titers were within 1 : 67-1 : 100. The lysozyme activity of the experimental dogs reached this level only on the 100th day after the flight. /84

The lysozyme activity of the integument was also considerably reduced in both animals. Attention was drawn to the lysozyme activity of the urine. It was established that lysozyme was contained in the urine of both dogs in quantities of 0.18 and 0.27 mg/ml on the third day after the flight. This testifies that in this period the renal barrier was permeable to low-molecular proteins such as lysozyme. Its molecular weight varies from 14,800 to 25,000.

Results of clinical examination of the animals' digestive systems does not allow us to consider that the metabolic disturbances occurring during the space flight were based on decrease in the function of the gastrointestinal tract, a decrease that could have led to deterioration of utilization of nutritive substances. Determination of the average daily dry residue and the nitrogen content in the feces indicates sufficiently high assimilability of the food. Neither did analysis of the dogs' gastric juice in the postflight period reveal substantial changes. However a sharp increase in the intestinal enzymes enterokinase and alkaline phosphotase was discovered in investigation of the enzymic activity of the feces. This was

evidently caused by a considerable shift in the enzyme-forming systems.

Occurrences of hemorrhagic diathesis expressed in the presence of erythrocytes in the animals' urine and feces were noted in both dogs after the flight.

Study of vascular permeability conducted using a tagged hippuran radioisotope (T^{131}) revealed disturbance of the permeability of the histo-hematic barriers accompanied by exit of not only proteins, but also formed elements from the blood stream. /85

Investigations of the mineral composition of bone tissue conducted by the x-ray photometry (densitometry) method are interesting. X-ray photographs of three sections of the dogs' calcanei were made on the second day after landing. A 10-11% decrease in the mineral saturation of these sections of the bones was discovered here. This is in accordance with results from investigation of the water-salt balance, results that revealed a heightened quantity of calcium in the animals' blood plasma.

Disturbances in the blood's coagulative system were expressed in an increase in fibrinogen content and a decrease in the amount of heparin and heparin-like substances, leading to heightening of the blood's coagulative capacity.

Morphological and histochemical examinations were carried out in the postflight period with biopsy of the liver, skeletal muscle and skin.

Study of the structure of the hepatic parenchyma and its histochemical peculiarities according to the data from punch biopsies performed on the second and tenth days after the flight showed retention of the normal structural relationships and histochemical properties of the liver. A large quantity of glycogen, the usual content of proteinic substances and high RNA content in the nucleoli were discovered in liver cells. This testifies to the intensive metabolism of hepatic tissue, which was only possible with full-valued nutrition and adequate oxygenation of liver tissue.

Study of a biopsy of the skin obtained two days after the flight revealed preservation of the epidermis and skin derivatives. The cells of the growth layer of the epidermis were loaded with glycogen and their cytoplasm was rich in RNA and had a positive reaction to proteins. Biopsy of the thigh muscle revealed muscle fibers retaining their transverse striations and fibrular structure. There were mild edema and perivascular hystocytic infiltrates in soft muscle tissue.

Therefore, analysis of the data obtained in an experiment on the Cosmos-110 artificial earth satellite has shown that when a highly-developed organism stays a comparatively long time under flight conditions (more than 20 days), there take place qualitatively new and more pronounced shifts in the animals' condition. The phenomena noted (30% loss in weight, disturbance of ion equilibrium, evidently related to loss of water by tissues and a number of other changes) were highly substantial. This allows us to think that it is necessary to use protective measures in future prolonged space flights.

Naturally, the data obtained on animals are necessarily transferred to the human organism with a certain caution. However the assertion is not unfounded that the nature and direction of the shifts, which are determined by common biological regularities, will be identical.

The report summarizes the material of colleagues who have taken part in the preparation and conduct of the experiment on the Cosmos-110 artificial earth satellite: Anashkina, O. D., Biryukova, Ye. M., Yegorova, B. B., Knyazevoy, G. D., Kotovoy, I. N., Kozar', M. I., Kozyrevskoy, G. I., Nikolayeva, S. O., Popova, N. N. and others.

Discussion

Ingvar: Could the ataxia you observed in the Cosmos dogs be related to the limited space in which they were living in the capsule, i.e. a deconditioning of their motor apparatus in the small place? Secondly, I would like to know whather your controls of the oxygen pressure showed that the animals had not been exposed to brain anoxia, not even during re-entry and that the ataxia observed could not be caused by such a factor?

Gurovskii: Before the flight the dogs were trained long enough and with sufficient care, they were markedly restrained in their movements, but they were habituated to this. Besides, ground experiments during which all flight conditions were fully reproduced, carried out on 4 dogs, showed no motion disturbances following the experiment. Thus the restriction of movements is not the only factor to be taken into consideration.

As to the second question—we have no indication of hypoxia. The oxygen content in the cabin was continuously monitored by telemetry; it could not have been provoked either by the strain imposed upon the organism during the re-entry phase of the flight, as this possibility was repeatedly checked by centrifuge experiments.

Bourne: Will the speaker please confirm that the duration of the flight of Cosmos 110 was three weeks, or was it longer?

Gurovskii: Almost 22 days (21 days and 18 hours).

Whiteside: Did the dogs hold the head too high or too low after return to earth. (You mentioned that there were swinging movements.)

Gurovskii: There were indeed lateral pendular movements of the head but these lasted only 2–3 days. The neural mechanism is not clear.

Egorov: The experiment was based on the hypothesis that rearrangement of the reflex regulation of some automatic function is to be expected after the elimination of certain central mechanisms depending to a smaller or greater extent on the force of gravity (reticular formation of the brain stem, hypothalamus, motor cortex and other). During the experiment the carotid sinus was stimulated and the reaction of the cardiovascular system followed. Changes in the reflex served for evaluating the functional re-arrangements. As a result of the flight we obtained data on the onset of stabilization of functions by the 16th day of flight. On the ground, after the flight, the re-adaptation of the organism has been studied. We have investigated the stabilization of the physiological functions—the recovery of motion, of body weight and of the regulation of autonomic functions.

2. For blood sampling and arterial tension measurements we had at our disposal an implanted catheter. A method has been developed allowing the implantation of the catheter for long periods.

Montandon: What is the role of vestibular afferents in the neurovegetative syndrome you have described in relation to weightlessness (otolithic in particular)? Isn't there a similarity with the vestibular vasodepressive syndrome and its secondary effects, particularly on the endocrine system, such as the effect, known in airline pilots, on the pituitary-adrenal axis? Have you carried experiments (in space) on labyrinthectomized animals?

Gurovskii: We think that the vestibular analyzer together with other analyzers takes part in the syndrome of changes found in space-flight. It can be assumed that the relationship between space analyzers is altered and that this is the cause of a number of changes.

We have not carried out experiments involving the destruction of the labyrinth.

Helvey: Gurovskii made the important conclusion that "protective measures" must be taken to combat the "substantial changes" observed in the Cosmos 110 animals. What protective mechanisms does he anticipate using to modify the effects of prolonged weightlessness?

Gurovskii: Data obtained during the Cosmos 110 flight speak of changes concerning a number of physiological systems. As to the necessity of protective measures, we would like to call attention to this problem. It appears that these protective measures should concern the widest scope of problems, starting with physical, pharmacological and other; some were mentioned in the paper by B. B. Egorov.

Grandpierre: I was very interested in the magnificent report which brought a number of precisions on the effects of prolonged weightlessness. In spite of the few functional disturbances concerning the heart, one is brought to think that it is the low tension circulation which is particularly disturbed, and I would like to have the opinion of Dr Gurovskii on the possible disturbances of the pulmonary circulation which we intend to try to study in the course of simulated weightlessness or during the short periods of weightlessness in rockets. Besides, since we are talking on local circulation, have you studied the cerebral circulation?

Gurovskii: In the Cosmos 110 space cabin the barometric pressure was normal, so that one cannot speak of reduced pressure and link circulatory disturbances to low external pressure. In the described experiment changes of the pulmonary circulation were not studied. I would rather not express my views on this subject since I do not have experimental data concerning it.

Jensen: With reference to Cosmos 110:

1. Were you able to obtain blood samples during the period of space flight in Cosmos 110?
2. What were the conditions of gas environment?
3. Was the elevated hemoglobin level a result of the decreased plasma volume, or the consequence of an absolute increase in red cell mass?

Gurovskii: 1. During the flight of Cosmos 110 it was possible to take blood samples.

2. The gas composition of the atmosphere in the cabin was practically analogous to that on the ground. The barometric pressure in the cabin amounted to about one atmosphere, the concentration of oxygen was 21–23%, that of CO_2 was not greater than 1%. The temperature of the air was 20–21%, etc. I am quoting the numbers by memory only, and they may be slightly different. Data on the composition of the atmosphere in the cabin, on pressure, temperature, humidity were sent on ground through telemetry channels during the whole flight.

2. The changes of hemoglobin are linked presumably to the peculiarities of water and mineral metabolism.

Welch: As noted in the discussion on Cosmos 110, the dogs lost approximately 26 and 29% of their body weight. What was the rate of recovery of this body weight loss? What do you calculate the composition of this weight loss to be?

Gurovskii: I have already given in my report the numerical data concerning body weight and its recovery. The recovery of one half of the weight loss occurred sufficiently rapidly (by day 9) and was linked to the recovery of water. Thereafter, the weight increased slowly, and the recovery was completed some 30 days after the flight. This was presumably the component which depended on muscular atrophy.

Gauer: The discoordination of the gait of animals after 21 days of weightlessness is very remarkable. I would guess that it is attributable to a disturbance of Sherington's antigravity reflex system. Would it be feasible to keep fast growing animals in the weightless condition for the period of time which it takes for the maturation of this part of the CNS, and see whether it would be possible for these animals to learn normal locomotion at return to a gravitational field, or whether the damage is irreversible?

Gurovskii: It is very difficult to answer this complicated question, since it is not possible at the present time to simulate the conditions of weightlessness on the ground, and the realization of such an experiment under space condtions will be possible in a rather distant future. The theoretical assumptions of Professor Gauer are very interesting.